REMARKS

Claims 18-21 and 24-31 are currently pending in this application.

Claims 19 and 21 have been withdrawn from consideration as being directed to non-elected species.

Claims 1-17, 22 and 23 have been cancelled without prejudice.

Claims 18-21 and 24 have been amended.

Claims 26-31 have been added. New claims 26-31 are readable upon the elected species. Claims 26, 27, 28, and 30 are generic linking claims.

Claims 18, 20, and 24-31 are under examination with respect to the elected species of FVIII polypeptides comprising the epitope of residues 817-831 of SEQ ID NO:73 having the V823A substitution.

Claim 18 has been rewritten in independent form to avoid dependency upon cancelled claim 17. Claim 18 has also been amended to clarify that at least one of the amino acids at the specified portions of SEQ ID NO:73 has been replaced by a different amino acid (i.e. one that is not present in the wild-type Factor VIII at the given position).

Claims 19-21, and 24 have been amended to replace dependency upon cancelled claim 17 with dependency upon rewritten claim 18.

An Information Disclosure Statement is submitted herewith as suggested by the Examiner.

The specification has been amended for clarity and to correct the obvious typographical errors identified by the Examiner. No new matter has been added.

In response to the objection to drawings, Applicant draws the Examiner's attention to replacement drawings of Figures 1 and 10 described on page 25 of the Preliminary Amendment filed on October 15, 2004, and submitted therewith. The referenced replacement drawing for Figure 1 contains SEQ ID numbers for each of the multitude of sequences listed therein. These replacement drawings appear on the PAIR system as an 11 page document directly above the 1 page document entitled "Applicant Arguments/Remarks

Made in an Amendment" (both filed on 10-15-2004). Accordingly, Applicants request that the objection be withdrawn.

Claims 18, 20, 24, and 25 stand rejected as allegedly being directed to non-statutory subject matter under 35 U.S.C. § 101. Examiner suggested using the term "isolated" in the rejected claims to overcome this rejection. Claim 18, which already claims "an isolated polypeptide," contains appropriate language to indicate the involvement of the hand of man, and thus should not have been included in the 35 U.S.C. § 101 rejection. Claims 20 and 24-26 depend upon Claim 18 and thus also contain the "isolated" language. New claims 27-31 also contain "isolated" language. Accordingly, claims 18, 20, and 24-31 meet the requirements of 35 U.S.C. § 101.

Claim 20 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In response, Claim 20 has been amended to indicate one substitution can occur at position 823 of the claimed polypeptide.

Enablement Rejection

Claims 18, 20, 24, and 25 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The rejection of claims 18, 20, 24 and 25 under 35 U.S.C. 112, first paragraph, is traversed.

Page 11 of the present Office Action sets forth a number of alleged "facts," but does not provide any references or evidence to support their factual nature. Even assuming that these assertions are "facts," claims 18, 20, and 24-26 are enabled.

The enablement rejection appears to be based, in part, upon the premise "that different class II molecules bind different peptide sequences and that the particular class II alleles bound by epitopes of the instant invention are not recited." As disclosed in the application, the *in silico* process used to identify potential T-cell epitopes can test the peptide sequence using >40 allotypes simultaneously. (Application p. 16, l. 1-13). The *in silico* methods taught by the various patents referenced in this application, including WO 02/069232, consider the binding properties of the roughly 76 human HLA-DR allotypes. Thus, there is no need to delineate specific allotypes to have enabled one of ordinary skill in

the art to practice the claim and methods.

The Examiner also bases the enablement rejection, in part, upon the premise "that the breadth of applicant's claims reads on mutations to FVIII in general as well as in specific locations." Claims 1-5 and 8-11, which are the only claims to which this particular argument could have applied, have been cancelled, and thus this point appears to be moot.

This enablement rejection also appears to be based, in part, on the erroneous assertion that page 41, lines 34-35 of the present application discloses that amino acids A, C, D, E, K, N, P, Q, R, S, and T can serve as potential primary anchor residues, and that substituting these amino acids would not reduce the immunogenicity of FVIII. In fact, this section of the specification identifies these amino acids as amino acids that do not serve as potential primary anchor residues. Page 41 of the specification has been amended to clarify this point. The language used in the amendment is consistent with the language used in other parts of the specification (*see, e.g.* page 40, line 22 of the original application) and does not add new matter. Therefore, the application teaches that amino acid substitutions at position 823 of FVIII using the identified amino acids would create a less immunogenic FVIII. The specification clearly would have enabled one of ordinary skill in the art at the time the invention was made to create a less immunogenic FVIII using the claimed amino acid substitutions.

The enablement rejection also appears to be based, in part, upon concerns about the alleged lack of experimental evidence showing that the amino acid sequences identified by computer program are actual T-cell epitopes that bind to MHC class II molecules. The claims require a reduction in immunogenicity, but do not require a reduction in actual binding of MHC class II molecules, however. The application states that "physical testing of the exemplary variant peptide epitopes using *ex vivo* human T-cell biological proliferation assays confirm the desired loss of ability for these peptides to support T-cell proliferation . . ." (Application page 23, ll. 4-6). One of these exemplary variant peptides is peptide P7, which contains amino acid V823. (Application page 21, l. 35 - page 22, l. 8). This *ex vivo* testing confirmed that the variant peptides of this application had a reduction in T-cell

proliferation, which is accepted to be correlated to reduced immunogenicity. Specific data related to the physical testing of peptide P8 also is disclosed at Fig. 8. Based upon these teachings, a skilled artisan would have been able to make and use the claimed invention without undue experimentation at the time the invention was made.

Regardless, Claim 18 and dependent claims 20, 24, 25 and 26 set forth specific amino acid positions in SEQ ID NO: 73 that will reduce immunogenicity as indicated by a reduction in T-cell proliferation activity. (See, e.g., Application p. 23, l. 35). Accordingly, the specification would have enabled one of ordinary skill to make and use the invention as it is claimed in Claims 18, 20, and 24-26.

Although Applicants disagree with the Examiner's reasoning for this rejection under 35 U.S.C. § 112, first paragraph, new claims 27-31 have been added to advance prosecution of this application. New claims 27-31 clearly comply with the enablement requirement. Claims 27-31 claim an amino acid alteration that eliminates at least one amino acid sequence identified by *in silico* modeling techniques as a potential T-cell epitope. The specification teaches one skilled in the art *in silico* modeling techniques to identify potential T-cell epitopes. (See, e.g., Application page 3, ll. 22-33; page 15, l.26- page 16, l. 25; Fig. 9). Whatever the actual mechanism of action may be, the specification teaches that elimination of these "potential T-cell epitopes" results in reduced immunogenicity. This teaching is supported by the *ex vivo* T-cell proliferation testing, which is correlated with reduced immunogenicity. Thus, concerns caused by the alleged unpredictability of using computer programs to identify actual T-cell epitopes and the lack of experimental MHC class II binding data are immaterial to newly added claims 27-31. Claims 27-31 claim modified Factor VIII proteins that include amino acid residue substitutions which are identified by computer modeling techniques to eliminate potential T-cell epitopes. The claims do not require that actual epitopes be eliminated. Rather, the claims only require that immunogenicity be reduced. The specification teaches that the claimed substitutions will do just that.

The pending claims as amended, including newly added claims 27-31, comply with the 35 U.S.C. § 112, first paragraph, enablement requirement.

Written Description Rejection

Claims 18, 20, 24, and 25 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The rejection of claims 18, 20, 24 and 25 under 35 U.S.C. § 112, first paragraph, is traversed.

The written description rejection appears to be based, in part, on the premise that the claims "broadly read on all FVIII molecules that contain an amino acid sequence that is different from wild type FVIII such that binding of a T cell epitope to an MHC class II molecule is reduced or eliminated." Cancelled claims 1-5 and 8-11 are the only claims with the breadth described above, and thus this point is moot.

The rejection also appears to be based upon concerns about the lack of experimental data verifying the accuracy of the computer predictions with regard to MHC class II binding. As discussed above in response to the enablement rejection, the specification teaches that modification in the exemplary peptide sequences confirmed a reduction in T-cell proliferation activity using *ex vivo* testing. The application also discloses testing for normal expression and activity for a FVIII molecule with an altered amino acid at position V823. (Application page 41, l. 31 - page 43, l. 3). Thus, the specification shows that the Applicants are in possession of the invention as it is claimed in Claims 18, 20, and 24-26, regardless of the biological mechanism by which the claimed peptides actually achieve reduced immunogenicity .

Although Applicants disagree with the Examiner's reasoning for this rejection under the written description requirement of 35 U.S.C. § 112, first paragraph, new claims 27-31 have been added to advance prosecution of this application. New claims 27-31 clearly comply with the written description requirement. Claims 27-31 claim an amino acid alteration that eliminates at least one amino acid sequence identified by *in silico* modeling techniques as a potential T-cell epitope. The specification contains information to show that the applicant was in possession of the claimed *in silico* modeling techniques used to identify

potential T-cell epitopes. (See, e.g., Application page 3, ll. 22-33; page 15, l.26- page 16, l. 25; Fig. 9). This teaching, coupled with the confirmed *ex vivo* reduction in T-cell proliferation for the exemplary peptides is sufficient to show that the Applicants were in possession of the claimed invention at the time the application was filed.

The pending claims as amended, including newly added claims 27-31, comply with the 35 U.S.C. § 112, first paragraph, written description requirement.

Prior Art Rejections

Claims 1 and 11 were rejected under 35 U.S.C. § 102(b) as being anticipated by Tiarks *et al.* This rejection is moot because claims 1 and 11 have been cancelled.

Claim 24 stands rejected under 35 U.S.C. § 102(a) as being anticipated by Jacqueim *et al.* The rejection is also not applicable with regard to claim 24 because claim 24 has been amended to depend upon claim 18 which was not included in this ground for rejection.

Claim 24 stands rejected under 35 U.S.C. § 102(a) and (e) as being anticipated by WO 02/098454 A2. The rejection is not applicable with regard to claim 24 because claim 24 has been amended to depend upon claim 18 which was not included in this ground for rejection.

Claim 24 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Tiarks *et al.* in view of Laub *et al.* The rejection is not applicable with regard to claim 24 because claim 24 has been amended to depend upon claim 18 which was not included in this ground for rejection.

Allowance of all claims and passage of the application to issue is solicited.

Respectfully submitted,

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